DETERMINING CANCER-LINKED GENES AND THERAPEUTIC TARGETS USING MOLECULAR CYTOGENETIC METHODS

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This application claims priority of U.S. Provisional Application Serial No. 60/550,304, filed 8 March 2004, the disclosure of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

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The present invention relates to Identification of amplifications / gains of genomic segments of DNA within human chromosomes in diseased states, such as cancer, that are demarcated and limited within specific chromosomal bands and defined herein as "amplicons" and whose disruption and/or change in expression is useful to distinguish cancerous from non-cancerous tissue and serve as potential therapeutic targets, pharmacodynamic /pharmacogenetic/surrogate and prognostic and diagnostic markers.

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BACKGROUND OF THE INVENTION

Malignant tumors are a leading cause of death in the United States and one in four Americans is likely to die of cancer. This disease is often characterized by an increase in the number of abnormal, neoplastic cells that are ultimately derived from a normal tissue after which the cells proliferate to form a tumor, which can then metastasize (spreading into adjacent tissues or traveling elsewhere in the body via the bloodstream or lymphatic system).

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The genomes of various well-studied tumors carry several different independently altered genes, including activated oncogenes and inactivated tumor suppressor genes. Chromosomal abnormalities have been identified in most cancer cells. Conventional chromosome banding techniques allow for the detection of specific chromosomal defects in tumor cells but interpretation of the banding pattern is sometimes difficult, particularly when complex chromosomal rearrangements or subtle abnormalities are present. In recent years, new techniques, such as CGH and SKY, based on fluorescent in situ hybridization (FISH) (Pinkel et al., Proc Nat Acad Sci USA 85:9138-42 (1988)) have been developed to overcome the limitations of conventional chromosome banding. CGH measures intensities of fluorescently labeled tumor DNA and normal DNA following hybridization to normal chromosomes (Kallioniemi et al., Science 258:818-21 (1992)). Gain or loss of copy number of a particular chromosome or chromosome region in the tumor DNA is determined by the relative intensity of a fluorescence ratio. SKY utilizes a cocktail of chromosome probes, fluorescently labeled to specify each chromosome, which is hybridized to tumor chromosomes in an effort to identify numerical and structural abnormalities in the tumor cell (Schröck et al., Science 273:494-7 (1996)). CGH and SKY have been used to identify chromosomal regions that harbor genes significant to the process of tumor initiation or progression.

The identification of amplifications of genomic DNA within well defined and demarcated limits on human chromosomes is done at a resolution of human chromosome banding limited to 400-550 bands by the technique of Comparative Genomic Hybridization (CGH). The present invention applies custom protocols to obtain human template chromosomes that are resolved to 850 to 1000 band resolution of human chromosomes (ISCN, 1985), to perform CGH on a large number of cell lines/ tissue samples/tumor cells. This allows the identification of regions of genomic DNA amplifications ranging from 2-5 Mbp at the highest limits of resolution of human chromosomes, detected by fluorescent intensity evaluations performed at the microscope.

Amplicons, or regions of interest,, from 10-20 Mb and more are also defined by these methods. These amplicons contain a gene, or genes, that are amplified (meaning copy number gains), and/or differentially expressed in the tissue/ cells of origin. Genes identified as being amplified and/or over-expressed provide targets for intervention with a small molecular therapeutic, antibodies, anti-sense or other therapeutic modalities. A gene or genes within these regions could also be used for diagnostic or prognostic molecular pathology characterization and useful as pharmacodynamic biomarkers for drug response profiling and patient sub-set selection and stratification.

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BRIEF SUMMARY OF THE INVENTION

In one aspect the present invention relates to a set of genes that have been localized within human chromosomal regions of interest (ROI) that have been identified by molecular cytogenetic techniques. In particular, the present invention relates to chromosomal regions of interest, or amplicons, that are summarized in Table 1 and containing genes corresponding to cDNA sequences shown in the sequence listing described herein.

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In another aspect, the present invention relates to a method for diagnosing the presence of a cancerous condition, or diagnosing a predisposition to developing a cancerous condition, in an animal, especially a human being, by determining the amplification and/or over-expression, of one or more genes corresponding to SEQ ID NO: 1-3049 in a cell, or tissue sample, obtained from an animal. The animal may be afflicted with, or at risk of developing, such a cancerous condition, or otherwise predisposed to develop such a condition.

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In a further aspect, the present invention relates to a method for the treatment of a cancerous condition, especially one involving breast, colon, lung, cervix, kidney, pancreas and prostate tissues, utilizing selected chemical

agents having anti-tumor activity as identified using one of the assays disclosed herein.

Thus, in one aspect the present invention relates to a method for identifying an antineoplastic agent, comprising:

- (a) contacting a test compound with a cell that expresses at least one gene corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 3049 and under conditions promoting expression of said gene; and
- (b) determining a change in expression of said gene as a result of said10 contacting

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wherein a change in expression indicates gene modulation thereby identifying said test compound as a gene modulating agent. In a preferred embodiment thereof, the change in expression is a decrease in expression.

In a further aspect, the present invention relates to a method for identifying a compound as an anti-neoplastic agent, comprising:

- (a) contacting a test compound with a polypeptide encoded by a gene selected from SEQ ID NO: 1-3049,
- (b) determining a change in a biological activity of said polypeptide due to said contacting,

wherein a change in activity indicates anti-neoplastic activity and thereby identifies such test compound as an agent having antineoplastic activity.

Preferably, the change in biological activity is a decrease in biological activity. Also preferred is where the biological activity is an enzyme activity, most preferably involving an enzyme selected from kinase, protease, peptidase, phosphodiesterase, phosphatase, dehydrogenase, reductase, carboxylase. transferase, deacetylase and polymerase. Also preferred is a biological activity that is a membrane transport activity, an integrin, a Cytochrome P450 enzyme, a nuclear hormone receptor, or a receptor activity,

such as a G-protein-coupled receptor. In other preferred embodiments, the polypeptide is contained in a cell.

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The present invention also relates to a method for treating cancer comprising contacting a cancerous cell with an agent first identified as having gene modulating activity using any of the methods of the invention and in an amount effective to cause a reduction in cancerous activity of said cell. In a preferred embodiment, said cancerous cell is contacted *in vivo*, as where the agent is administered to a mammal, especially a human being, afflicted with cancer and in an amount sufficient to ameliorate the cancer.

The present invention further relates to a method for treating cancer comprising contacting a cancerous cell with an agent having affinity for an expression product of a gene corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1-3049 and in an amount effective to cause a reduction in cancerous activity of said cell. Preferably, the expression product is a polypeptide and the agent is an antibody.

The present invention also relates to a method for monitoring the progress of cancer therapy in a patient comprising monitoring in a patient undergoing cancer therapy the expression of a gene corresponding to a polypeptide having a sequence selected from SEQ ID NO: 1-3049, preferably wherein the gene comprises a sequence of SEQ ID NO: 1-3049, such as where the cancer therapy is chemotherapy.

In a further embodiment, the present invention relates to a method for determining the likelihood of success of cancer therapy in a patient, comprising monitoring in a patient undergoing cancer therapy the expression of a gene corresponding to a polynucleotide having a sequence of one or SEQ ID NO: 1 – 3049 wherein a decrease in said expression prior to completion of said cancer therapy is indicative of a likelihood of success of said cancer

therapy, preferably wherein the gene comprises a sequence of SEQ ID NO: 1-3049 and wherein the cancer therapy is chemotherapy.

The present invention still further relates to a method for determining the progress of a treatment for cancer in a patient afflicted therewith, following commencement of a cancer treatment on said patient, comprising:

- (a) determining in said patient a change in expression of one or more genes corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 3049; and
- (b) determining a change in expression of said gene compared to expression of said one or more determined genes prior to commencement of said cancer treatment;

where in said change in expression indicates progress of said treatment thereby determining the progress of said treatment. Preferred embodiments include where the change in expression is a decrease in expression and said decrease indicates success of said treatment.

20 **DEFINITIONS**

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As used herein, the following terms have the indicated definition unless expressly stated otherwise.

The term "amplicon" refers to regions of interest, i.e., genomic segments of DNA within human chromosomes in diseased states like cancer that are demarcated and limited within specific chromosomal bands. Since these amplicons contain sequences of a gene/ or genes that are amplified (copy number gains), and/ or differentially expressed in the tissue/ cells of origin, a listing of these genes within the amplicons detected are listed in Table 3. Genes identified as being amplified and/or over-expressed within the amplicons provide a useful target for intervention with small/large

molecule/protein/antibody therapeutics, anti-sense or other therapeutic modalities. A gene or genes within these regions is also useful for diagnostic or prognostic molecular pathology characterization/companion diagnostics, and useful as pharmacodynamic biomarkers for drug response profiling and patient sub-set selection and stratification.

The term "percent identity" or "percent identical," when referring to a sequence, means that a sequence is compared to a claimed or described sequence after alignment of the sequence to be compared (the "Compared Sequence") with the described or claimed sequence (the "Reference Sequence"). The Percent Identity is then determined according to the following formula:

Percent Identity = 100 [1-(C/R)]

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wherein C is the number of differences between the Reference Sequence and the Compared Sequence over the length of alignment between the Reference Sequence and the Compared Sequence wherein (i) each base or amino acid in the Reference Sequence that does not have a corresponding aligned base or amino acid in the Compared Sequence and (ii) each gap in the Reference Sequence and (iii) each aligned base or amino acid in the Reference Sequence that is different from an aligned base or amino acid in the Compared Sequence, constitutes a difference; and R is the number of bases or amino acids in the Reference Sequence over the length of the alignment with the Compared Sequence with any gap created in the Reference Sequence also being counted as a base or amino acid.

If an alignment exists between the Compared Sequence and the Reference Sequence for which the percent identity as calculated above is about equal to or greater than a specified minimum Percent Identity then the Compared Sequence has the specified minimum percent identity to the Reference Sequence even though alignments may exist in which the

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hereinabove calculated Percent Identity is less than the specified Percent Identity.

As used herein, the terms "portion," "segment," and "fragment," when used in relation to polypeptides, refer to a continuous sequence of residues, such as amino acid residues, which sequence forms a subset of a larger sequence. For example, if a polypeptide were subjected to treatment with any of the common endopeptidases, such as trypsin or chymotrypsin, the oligopeptides resulting from such treatment would represent portions, segments or fragments of the starting polypeptide. When used in relation to a polynucleotide, such terms refer to the products produced by treatment of said polynucleotides with any of the common endonucleases, or any stretch of polynucleotides that could be synthetically synthesized.

As used herein, the term "DNA segment" or "DNA sequence" refers to a DNA polymer, in the form of a separate fragment or as a component of a larger DNA construct, which has been derived from DNA, and may include both single stranded and duplex sequences. Such segments are provided in the form of an open reading frame uninterrupted by internal non-translated sequences, or introns, which are typically present in eukaryotic genes.

The term "coding region" refers to that portion of a gene which either naturally or normally codes for the expression product of that gene in its natural genomic environment, i.e., the region coding *in vivo* for the native expression product of the gene.

The term "nucleotide sequence" refers to a heteropolymer of deoxyribonucleotides. Generally, DNA segments encoding the proteins provided by this invention are assembled from cDNA fragments and short oligonucleotide linkers, or from a series of oligonucleotides, to provide a synthetic gene which is capable of being expressed in a recombinant

transcriptional unit comprising regulatory elements derived from a microbial or viral operon.

The term "expression product" means that polypeptide or protein that is the natural translation product of the gene and any nucleic acid sequence coding equivalents resulting from genetic code degeneracy and thus coding for the same amino acid(s).

The term "fragment," when referring to a coding sequence, means a portion of DNA comprising less than the complete coding region whose expression product retains essentially the same biological function or activity as the expression product of the complete coding region.

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DETAILED SUMMARY OF THE INVENTION

The present invention relates to a set of genes that are amplified and/or over-expressed genes in cancer cell lines and have been localized to various chromosomal regions of interest. These genes have been identified through a combination of CGH, SKY, expression analysis and Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR). Such genes are both markers and potential therapeutic targets for cancer, in particular breast; colon, lung and prostate malignancies. In addition, the amplified nature of such genes provides a means of diagnosing a cancerous condition, or predisposition to a cancerous conditions, by determining the amplification of one or more of such genes in a patient afflicted with, or predisposed toward, or otherwise at risk of developing, cancer.

In one aspect the present invention relates to a set of genes that have been localized within human chromosomal regions of interest (ROI) that have been identified by molecular cytogenetic techniques. In particular, the present

invention relates to chromosomal regions of interest, or amplicons, that are summarized in Table 1. Table 2 lists tissues where the amplicons are found, cell lines expressing them, the amplification ratios found in those tissues for cancer versus normal cells, amplicon size and the chromosomal locations of the amplicons. Table 3 lists the chromosomal locations and accession number identifications of these regions of interest and which serve to correlate amplicons with the cDNA sequences of SEQ ID NO: 1-3049.

10 Table 1 - List of Amplicons

	AMPLICON	CHR	BPSTART	BPEND	BPLENGTH
15	A1 A2 A3 A4	8 13 5 13	122000000 96500000 175000000 26500000	127500000 100000000 181500000 34000000	5500000 3500000 6500000 7500000
20	A5 A6 A7	7 10 7	101000000 73500000 71000000 116500000	106000000 82500000 77500000 120000000	5000000 9000000 6500000 3500000
	A8 A9 A10 A11	6 18 9	3600000 70500000 9000000	41000000 76500000 18500000	500000 500000 600000 9500000

For Table 1, CHR means chromosome number, BPLENGTH represents the number of nucleotides in the amplicon. BPSTART refers to "base pair start point" and BPEND refers to "base pair end point" along the chromosome based on the July 2003 human reference sequence UCSC version hg16 (NCBI Build 34).

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Table 2. Amplicon Locations

cell line	Amp #	tissue	chrom	band start	band stop	Ratio	amplicon size_MB	
HCC1954	A1	Breast	8	q24.13	q24.13	14	5.3	
NCI H446	A1	scLung	8	q24.13	q24.21	8	8.3	
NCI H827	A1	scLung	8	g24.13	q24.21	6	8.3	
HCC202	A1	Breast	8	q24.13	q24.21	6	8.3	
NCI H82	A1	scLung	8	q24.13	q24.13	7	5.3	
NCI H23	A1	nscLung	8	q24.13	q24.13	7	5.3	
MDA MB436	A2	Breast	13	q32.2	q32.3	6	5.3	
NCI H1963	A2	scLung	13	q32.3	q32.3	6	3.3	
EFM192A	A2	Breast	13	q32.3	q34	8	18.8	
MDA MB157	A2	Breast	13	q32.3	q34	5	18.8	
HCC1937	A2	Breast	13	q32.3	q32.3	4	3.3	
SKBR3	A2	Breast	13	q32.3	q32.3	4	18.8	
NCI H1963	A2	nscLung	13	q32.3	q32.3	6	3.3	
HCC1954	A3	Breast	5	q35.3	q35.3	4	4.3	
MDA_MB436	A3	Breast	5	q35.1	q35.3	7	14	
BT20	A4	Breast	5	q35.1	q35.3	4	14	
KPL1	A5	Breast	5	q35.1	q35.3	4	14	
HCC3153	A6	Breast	5	q35.3	q35.3	3	4.3	
HT29	A4	Colon	13	q12.3	q13.2	5	9	
SW403	A4	Colon	13	q21.1	q21.2	15	6	
BT20	A4	Breast	13	q12.3	q13.2	4	9	
CPDR9	A4	Prostate	13	q12.2	q12.3	2	7.1	
SW480	A5	Colón	7	q22.2	q22.2	9	7.2	
X71	A5	Colon	7	q22.1	q22.2	5	7.2 3.3	
X72	A5	Colon	<i>(</i>	q22.3	q22.3	6	3.3 7.2	
Lovo	A6	Colon	<i>[</i>	q22.1	q22.2	5 5	7.2 7.2	
X1819_1	A7	Colon	7	q22.1	q22.2	6	15.3	
EFM19	A6	Breast	10	q22.1	q22.3	7	8.3	
PC3	A6	Prostate	10	q22.2	q22.3 q22.2	3	10.7	
MDA_MB436		Breast	10	q22.1	q22.2 q22.3	4	8.3	
SKBR3	A6	Breast	10	q22.2 q22.1	q22.3	4	15.3	
SW48	A6	Colon	10 10	q22.1 q22.2	q22.3	2	8.3	
X71	A6	Colon	7	q22.2 q11.23	q22.3 q11.23		4	
SKBR3	A7	Breast	7	q11.23	q11.23		4	
X72	A7	Colon	7	q11.23			4	
X71	A7	Colon Colon	7	q11.23	q11.23		4	
X1819_1	A7 A7	scLung	7	q11.23	-		4	
NCI_H69	A7 A8	Breast	1	p12.2	p13.2		9	
BT20	A8	Breast	1	p12	p12	6	6.7	
CAMA-1 KPL-1	A8	Breast	1	p11.2	p13.3		14.7	
Colo205	A0 A9	Colon	6	p21.2	p21.2	_	3.4	
MDA MB231		Breast	6	p21.1	p21.2		9.8	
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NCI H522	A9	nscLung	6	p21.2	p21.31	6	9.1
PANC-1	A10	Pancreas	18	q23	q23	7	5.2
NCI H1607	A11	scLung	9	p22.2	p23	10	14.5
NCI H446	A11	scLung	9	p22.3	p22.3	8	2.9
HCC1954	A11	Breast	9	p22.2	p23	10	14.5

In addition, SEQ ID NO: 1-3049 represents the nucleotide sequences for cDNA sequences corresponding to genes located in these regions of interest. Such regions contain genes found to be amplified and over-expressed in cancerous tissues, especially of breast, colon, lung, cervix, kidney, pancreas and prostate.

Each amplicon may contain about 75 genes, at least one of which will be amplified in a cancerous condition. Genes that show amplification and/or over-expression can be indicative of the cancerous status of a given cell.

Briefly, the procedures used to identify the genes disclosed herein may be summarized as follows:

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For CGH analysis, based on detailed molecular cytogenetic characterizations, the following data sets are generated, which may include regions reported in the public domain as well as unique regions not previously known.

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1. A map of chromosomal regions involved in consistent, recurrent and high level genomic gains (i.e., amplifications) for a representative cancer cell line or tumor type (e.g. colon, prostate, breast and lung) that can be recognized as a pattern/signature for a given tumor type.

- 2. A map of chromosomal regions containing genomic losses (i.e., deletions) in each tumor type and individual cell line to be examined.
- 3. Levels of intensities of gains and losses categorized for entry into a database.

4. A comparison of the patterns of gains and losses between the clinical samples (e.g. colon xenografts) and cell lines (e.g., colon) of matched Stages and Grades.

5. A comparison of the patterns of gains and losses between primary prostate tumor cell lines (e.g., CPDR lines) and metastatic prostate tumor cell lines (e.g., DU 145, PC3 and LNCaP).

In accordance with the present invention, for SKY analysis, data sets were generated according to the following steps:

- 1. Identification and development of a database of novel chromosomal rearrangements in epithelial cancer cell lines.
- 2. Identification of novel translocations involving specific chromosomes or chromosomal regions
- 3. Reconciliation of SKY and CGH analysis on the same cell line as a verification of the combined findings.

Combining genomic DNA analysis of gains and losses in the tumor cell lines/clinical samples with cDNA expression analysis from matched tumor types displayed ordered on the assembled Human genome sequence :

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1 A pattern of gene expression on a Affymetrix chip set (U95 and U133) was used to generate differential gene expression profiles between samples sets containing normal and malignant tissues from colon, prostate, lung, breast and various cell lines.

2. A Spotfire™ visualization tool was developed that allowed the generation of a list of all the genes that are present in the Human genome sequence within the defined regions of gains/losses for each cell type/tumor type to identify genes to include in the HITS platform

and for identification of cancer associated genes

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3. The following algorithm was employed:

i) Match chromosomal regions of amplification/gains defined by CGH with the location of genes/ESTs on an Affymetrix chip as mapped to a Human genome template.

ii) Identify genes/ESTs over-expressed in tumor tissue compared to normal tissue in said chromosomal regions using.

iii) Compile data on cell lines of a particular tumor type and different tumor types showing clusters of genomic gains and losses at certain chromosomal regions.

Pick BACs that span the chromosomal regions consistently gained and containing over-expressed genes in an effort to positionally clone novel cancer genes (oncogenes and genes in relevant pathways)

Validate the identified genes by
A) Picking STS markers that identify the gene sequence and quantify the relative copy number in genomic DNA and RNA across a panel of tumor cell lines.

B) Develop probes for FISH on chromosomes from tumor cell lines and primary tumor tissue micro-arrays.

4. The expression data from tumor cell lines that have undergone SKY/CGH analysis was used to pick candidate genes to validate as individual targets in functional genomic assays and in-vivo assays and for use in the transcriptional assay platform.

In accordance with the present invention, over-expression of cellular genes is conveniently monitored in model cellular systems using cell lines (such as is used in the example below), primary cells, or tissue samples maintained in growth media. For different purposes, these may be treated with compounds at one or more different concentrations to assay for modulating agents. Thus, cellular RNAs are isolated from the cells or cultures as an indicator of selected gene expression. The cellular RNAs are then divided and

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subjected to analysis to determine the presence and/or quantity of specific RNA transcripts, which transcripts are then amplified for detection purposes using standard methodologies, such as reverse transcriptase polymerase chain reaction (RT-PCR). The levels of specific RNA transcripts, including their presence or absence, are determined. When used for identification of modulating agents, such as anti-neoplastic agents, a metric is derived for the type and degree of response of the treated sample compared to control samples.

In accordance with the foregoing, the amplicons identified as being amplified and/or over-expressed, which can include increased copy number thereof, in cancerous cells are localized in chromosomal regions of interest as identified in Tables 2 and 3.

The genes localized in these amplicons may be utilized to characterize, the cancerous, or non-cancerous, status of cells, or tissues. The methods of the invention may be used with a variety of cell lines or with primary samples from tumors maintained *in vitro* under suitable culture conditions for varying periods of time, or *in situ* in suitable animal models.

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The amplicons disclosed herein are expressed at levels in cancer cells that are different from the expression levels in non-cancer cells. Expression in cancer versus non-cancer cells of the same tissue type is a key identifier.

In accordance with the forgoing, the present invention also relates to a method for identifying a gene modulating agent, such as an anti-neoplastic agent, comprising:

(a) contacting a test compound, a compound whose gene-modulating and/or anti-neoplastic activity is to be determined, with one or more cells expressing one or more genes mapped to the chromosomal region of interest, or amplicon, for genes as identified in Table 3, and

(b) determining a change in expression of said one or more genes compared to when said contacting has not occurred,

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wherein a change in expression of said gene is indicative of gene modulating activity, thereby identifying said test compound as a gene modulating agent.

In accordance with the foregoing, the present invention relates to a method for identifying an antineoplastic agent, comprising:

- (a) contacting a test compound with a cell that expresses one or more amplicons of Table 2 having an amplification ratio of at least 2.0; and
- (b) determining a change in said amplification ratio due to said contacting;

wherein a change in said amplification ratio due to said contacting indicates that said test compound has gene modulating activity

thereby identifying said test compound as a gene modulating agent.

The present invention also contemplates a method for identifying an antineoplastic agent, comprising:

- (a) contacting a test compound with a cell that expresses at least one gene corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 3049 and under conditions promoting expression of said gene; and
- (b) determining a change in expression of said gene as a result of said contacting

wherein a change in expression indicates gene modulation thereby identifying said test compound as a gene modulating agent.

In preferred embodiments of these methods, the change in expression is a decrease in expression and/or the decrease in expression is a decrease in copy number of the gene and/or the gene comprises a nucleotide sequence of one of SEQ ID NO: 1-3049 and/or the cell was genetically engineered to express said gene.

Because the genes disclosed herein are over-expressed and relate to the cancerous condition of a cell, successful anti-neoplastic activity will commonly be exhibited by agents that reduce the expression of said genes In one embodiment thereof, the change in expression is a decrease in copy number of the gene or genes under study. In accordance therewith, said change in gene copy number is conveniently determined by detecting a change in expression of messenger RNA encoded by said gene sequence. In another preferred embodiment, expression is determined for more than one

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such gene, such as 2, 5, 10 or more of the genes.

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Thus, the present invention also encompasses a method for detecting the cancerous status of a cell, comprising detecting elevated expression in said cell of at least one gene corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 – 3049 whereby such elevated expression is indicative of cancerous status of the cell. In preferred embodiments thereof, the elevated expression is an elevated copy number of the gene.

Other methods useful in measuring a change in expression of the genes disclosed herein include measuring a change in the amount or rate of synthesis of a polypeptide encoded by said gene, preferably a decrease in synthesis of said polypeptide. Most preferably, the polypeptide comprises an amino acid sequence highly homologous to a sequence encoded by a gene mapping to an amplicon disclosed herein and whose expression is elevated in cancer.

The methods of the invention can thus be utilized to identify antineoplastic agents useful in treatment of cancerous conditions. Such activity can be further modified by first identifying such an agent using an assay as already described and further contacting such agent with a cancerous cell, followed by monitoring of the status of said cell, or cells. A change in status

indicative of successful anti-neoplastic activity may include a decrease in the rate of replication of the cancerous cell(s), a decrease in the total number of progeny cells that can be produced by said cancerous cell(s), or a decrease in the number of times said cancerous cell(s) can replicate, or the death of said cancerous cell(s).

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Anti-neoplastic agents may also be identified using recombinant cells suitably engineered to contain and express the cancer-related genes disclosed herein. In one such embodiment, a recombinant cell is formed using standard technology and then utilized in the assays disclosed herein. Methods of forming such recombinant cells are well known in the literature. See, for example, Sambrook, et al., Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor, N.Y., (1989), Wu et al, *Methods in Gene Biotechnology* (CRC Press, New York, NY, 1997), and *Recombinant Gene Expression Protocols*, in *Methods in Molecular Biology*, Vol. 62, (Tuan, ed., Humana Press, Totowa, NJ, 1997), the disclosures of which are hereby incorporated by reference.

The present invention also relates to a method for detecting the cancerous status of a cell, comprising detecting elevated copy number and/or expression in said cell of at least one gene that maps to a chromosomal region of interest, or amplicon, as identified in Table 3. Such elevated expression may be readily monitored by comparison to that of otherwise normal cells having the same genes. Elevated expression of such genes is indicative of the cancerous state. Such elevated expression, including increased copy number, may be the expression of more than one such gene.

The present invention also relates to a method for detecting a cancer-linked gene comprising the steps of contacting a test compound, identified as having gene modulating activity for a gene mapping to one of the amplicons disclosed herein, with a cell expressing a test gene and detecting modulation, such as decreased activity, of such test gene relative to when said compound

is not present thereby identifying said test gene as a cancer-related gene. In preferred embodiments, the gene determined by said method is an oncogene, or cancer facilitating gene.

In another embodiment, there is provided a method for treating cancer comprising contacting a cancerous cell with an agent first identified as having gene modulating activity using any of the assay methods disclosed according to the invention and in an amount effective to reduce the cancerous activity of said cell. In a preferred embodiment, the cancerous cell is contacted *in vivo*. In other preferred embodiments, said reduction in cancerous activity is a decrease in the rate of proliferation of said cancerous cell, or said reduction in cancerous activity is the death of said cancerous cell.

The present invention further relates to a method for treating cancer comprising contacting a cancerous cell with an agent having activity against an expression product encoded by a gene mapping to an amplicon as disclosed herein, preferably where the expression product is a polypeptide. In a preferred embodiment, said cancerous cell is contacted *in vivo*. In another preferred embodiment, the agent is an antibody.

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Nucleotide sequences mapping to the amplicons disclosed herein may be genomic in nature and thus represent the sequence of an actual gene, such as a human gene, or may be a cDNA sequence derived from a messenger RNA (mRNA) and thus represent contiguous exonic sequences derived from a corresponding genomic sequence or they may be wholly synthetic in origin for purposes of testing. Such cDNA sequences, mapping to the amplicons disclosed herein are identified as SEQ ID NO: 1-3049.

As described in the Example below, the expression of cancer-related genes may be determined from the relative expression levels of the RNA complement of a cancerous cell relative to a normal (i.e., non-cancerous) cell. Because of the processing that may take place in transforming the initial RNA

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transcript into the final mRNA, the sequences disclosed herein may represent less than the full genomic sequence. They may also represent sequences derived from ribosomal and transfer RNAs. Consequently, the genes present in the cell (and representing the genomic sequences) and the sequences disclosed in SEQ ID NO: 1-3049, which are mostly cDNA sequences, may be identical or may be such that the cDNAs contain less than the full genomic sequence. Such genes and cDNA sequences are still considered corresponding sequences because they both encode similar RNA sequences. Thus, by way of non-limiting example only, a gene that encodes an RNA transcript, which is then processed into a shorter mRNA, is deemed to encode both such RNAs and therefore encodes an RNA complementary to (using the usual Watson-Crick complementarity rules), or that would otherwise be encoded by, a cDNA (for example, a sequence as disclosed herein). Thus, the sequences disclosed herein correspond to genes contained in the cancerous or normal cells used to determine relative levels of expression because they represent the same sequences or are complementary to RNAs encoded by these genes. Such genes also include different alleles and splice variants that may occur in the cells used in the methods of the invention.

In addition, sequences encoding the same proteins as any of these genes, regardless of the percent identity of such sequences, are also specifically contemplated by any of the methods of the present invention that rely on any or all of said sequences, regardless of how they are otherwise described or limited. Thus, any such sequences are available for use in carrying out any of the methods disclosed according to the invention. Such sequences also include any open reading frames, as defined herein, present within any genes mapping to the amplicons of the invention.

The present invention also finds use as a means of diagnosing the presence of cancer in a patient, as where a sample of cancerous tissue or cells, or tissues or cells suspected of being cancerous, are examined for elevated expression, such as at least 2 fold expression, of a gene in one of

the amplicons disclosed herein, such as an increased expression of a cDNA sequence, or polypeptide encoded by said cDNA sequence, disclosed in Table 3 and being one of the sequences of SEQ ID NO: 1-3049.

For such purposes, and in accordance with the disclosure elsewhere herein, such diagnosis is based on the detection of elevated expression or amplification, such as elevated copy number, of one or more of the genes identified according to the invention. Such elevated expression can be determined by any of the means described herein.

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In one such embodiment, the elevated expression, as compared to normal cells and/or tissues of the same organ, is determined by measuring the relative rates of transcription of RNA, such as by production of corresponding cDNAs and then analyzing the resulting DNA using probes developed from genes mapping to the amplicons of the invention. Thus, the levels of cDNA produced by use of reverse transcriptase with the full RNA complement of a cell suspected of being cancerous produces a corresponding amount of cDNA that can then be amplified using polymerase chain reaction, or some other means, such as rolling circle amplification, to determine the relative levels of resulting cDNA and, thereby, the relative levels of gene expression.

For RNA analysis, the latter may be isolated from samples in a variety of ways, including lysis and denaturation with a pheno lic solution containing a chaotropic agent (e.g., triazol) followed by isopropanol precipitation, ethanol wash, and resuspension in aqueous solution; or lysis and denaturation followed by isolation on solid support, such as a Qiagen resin and reconstitution in aqueous solution; or lysis and denaturation in non-phenolic, aqueous solutions followed by enzymatic conversion of RNA to DNA template copies. Steady state RNA levels for a given type of cell or tissue may have to be ascertained prior to employment of the methods of the invention but such

is well within the skill of those in the art and will not be further described in detail herein.

Alternatively, increased expression, such as increased copy number, may be determined for the genes present in a cancerous cell, or a cell suspected of being cancerous, by determining elevated expression within the regions of interest, or amplicons, disclosed herein. Thus, the DNA of such cells may be extracted and probed for increased gene expression within the area disclosed herein as amplified in different cancer types and tissues.

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In employing the methods of the invention, it should be borne in mind that gene expression indicative of a cancerous state need not be characteristic of every cell found to be cancerous. Thus, the methods disclosed herein are useful for detecting the presence of a cancerous condition within a tissue where less than all cells exhibit the complete pattern of over-expression. For example, a set of selected genes, which are found within the regions of interest disclosed herein, may be found, using appropriate probes, either DNA or RNA, to be present in as little as 60% of cells derived from a sample of tumorous, or malignant, tissue while being absent from as much as 60% of cells derived from corresponding noncancerous, or otherwise normal, tissue (and thus being present in as much as 40% of such normal tissue cells). In a preferred embodiment, such gene pattern is found to be present in at least 70% of cells drawn from a cancerous tissue and absent from at least 70% of a corresponding normal, noncancerous, tissue sample. In an especially preferred embodiment, such gene pattern is found to be present in at least 80% of cells drawn from a cancerous tissue and absent from at least 80% of a corresponding normal, noncancerous, tissue sample. In a most preferred embodiment, such gene pattern is found to be present in at least 90% of cells drawn from a cancerous tissue and absent from at least 90% of a corresponding normal, noncancerous, tissue sample. In an additional embodiment, such gene pattern is found to be present in at least 100% of cells drawn from a cance rous tissue

and absent from at least 100% of a corresponding normal, non-cancerous, tissue sample, although the latter embodiment may represent a rare occurrence.

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Because changes in expression of these genes (up-regulation) are linked to the disease state (i.e. cancer), the change in expression may contribute to the initiation or progression of the disease. For example, if a gene that is up-regulated is an oncogene such a gene provides for a means of screening for small molecule therapeutics beyond screens based upon expression output alone. For example, genes that display up-regulation in cancer and whose elevated expression contributes to initiation or progression of disease represent targets in screens for small molecules that inhibit or block their function. Examples include, but are not be limited to, kinase inhibition, cellular proliferation, substrate analogs that block the active site of protein targets, etc.

It should be noted that there are a variety of different contexts in which genes have been evaluated as being involved in the cancerous process. Thus, some genes may be oncogenes and encode proteins that are directly involved in the cancerous process and thereby promote the occurrence of cancer in an animal. Other genes may simply be involved either directly or indirectly in the cancerous process or condition and may serve in an ancillary capacity with respect to the cancerous state. All such types of genes are deemed with those to be determined in accordance with the invention as disclosed herein. Thus, the gene determined by said method of the invention may be an oncogene, or the gene determined by said method may be a cancer facilitating gene, the latter including a gene that directly or indirectly affects the cancerous process, either in the promotion of a cancerous condition or in facilitating the progress of cancerous growth or otherwise modulating the growth of cancer cells, either in vivo or ex vivo. Such genes may work indirectly where their expression alters the activity of some other gene or gene expression product that is itself directly involved in initiating or

facilitating the progress of a cancerous condition. For example, a gene that encodes a polypeptide, either wild or mutant in type, which polypeptide acts to suppress of tumor suppressor gene, or its expression product, will thereby act indirectly to promote tumor growth.

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Many cancerous genes appear to have their effect by encoding an aberrant protein that functions in a cell in a manner different from that of normal cells, or else said protein is overproduced or underproduced as a result of some mutation in the coding sequence, or promoter or enhancer sequences, of a particular gene, such as one of Genes 1 – 3049 disclosed herein and expressed by the amplicons of the invention.

In accordance with the present invention, there are provided methods for measuring the activity, such as a biological activity, of such a polypeptide. Such biological activity may include any measurable activity, such as chemical reactivity, catalytic ability, binding to specific structures and receptors, acting as a receptor, or just being present in a membrane of a cell and therefore available as a target site for antibodies or other agents. Any such polypeptides may thus provide a target for a chemotherapeutic agent, especially an antineoplastic agent.

As is well known in the art, polypeptide activities can be measured in different ways so as to enable screening procedures for agents, such as test compounds, that inhibit the activity of the polypeptide and thereby work against the function of that polypeptide, such as where the polypeptide is some type of cancer-related protein, such as that produced by expression of an oncogene, or where the polypeptide is overproduced as part of the cancer initiating or facilitating process. As non-limiting examples, such screening methods for antineoplastic agents can include the measurement of compounds that bind to proteins (or that bind to a gene or a transcript of a gene), compounds that inhibit expression (including processing and/or maturation) of a protein, or the detection of downstream reaction product,

most often with specific antibodies using enzyme-linked immunosorbent assay (ELISA) procedures well known in the art, or compounds that inhibit activity, such as enzyme activity or some other function, or compounds that interact with upstream or downstream proteins (such as with transcription factors or other binding proteins that may serve to regulate gene expression).

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In accordance with the foregoing, the present invention relates to a method for identifying a compound as an anti-neoplastic agent, comprising:

- (a) contacting a test compound with a polypeptide encoded by a gene selected from SEQ ID NO: 1 3049,
- (b) determining a change in a biological activity of said polypeptide due to said contacting,

wherein a change in activity indicates anti-neoplastic activity and thereby identifies such test compound as an agent having antineoplastic activity.

In a preferred embodiment, the change in biological activity is a decrease in biological activity.

In another preferred embodiment, the biological activity is an enzyme activity, such as where the enzyme is one selected from the group kinase, protease, peptidase, phosphodiesterase, phosphatase, dehydrogenase, reductase, carboxylase. transferase, deacetylase and polymerase.

for such available, enzymes these are Assays for relevant pharmacologically phosphodiesterases most (the phosphodiesterases are those that hydrolyze cyclic nucleotides (see, for example, cAMP and cGMP assays available from Perkin-Elmer, as well as Estrade et al., Eur. J. Pharmacol. 352:2-3, 157-163 (1998)).

Protein phosphatases remove phosphate residues from proteins. Most tests of their activity use the same assays as for protein kinases. A non-radioactive phosphatase assay system is available from Promega Biotech.

The therapeutically most relevant dehydrogenases oxidize or reduce small molecular weight metabolites, esp. steroid hormones, or that generally use or generate NAD or NADP (see: Haeseleer et al., J. Biol. Chem., 273:21790-21799 (1998)). A commercial assay is available from Cayman Chemical (at www.caymanchem.com).

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Gamma-carboxylases are important enzymes in the blood coagulation process. The main assay protocols use synthetic peptides (see: Ulrich et al., J. Biol. Chem., 263:9697-9702 (1988); Begley et al., J. Biol. Chem., 275:36245-36249 (2000)).

In highly preferred embodiments, the kinase is one of a protein kinase, a serine or threonine kinase, or a receptor tyrosine protein kinase. Where the polypeptide encoded by a gene of the invention is a protein kinase, especially involving tyrosine kinase, various assays for activity are available. Protein kinases add phosphate groups to serine, threonine or tyrosine residues on proteins, most commonly measured with phospho-serine, threonine, or tyrosine-specific antibodies, or generation of radiolabeled substrate, or consumption of ATP, or phosphorylation of (synthetic) small peptides, or measuring downstream enzyme activity and gene transcription. Such assays are commercially available. (See, for example, the tyrosine kinase assay from Roche Molecular Biochemicals). Assays for serine/threonine kinases are also available at Chromagen.com, Upstate Biotechnology, Inc. (Lake Placid, NY, and at upstatebiotech.com) and from Applied BioSystems (Foster City, CA (home.appliedbiosystems.com)).

In other specific embodiments, the protease is a serine protease, cysteine protease or aspartic acid protease, or the transferase is a methyltransferase, preferably a cytosine methyltransferase or an adenine methyltransferase, or the deacetylase is a histone deacetylase, or the

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carboxylase is a γ -carboxylase, or the peptidase is a zinc peptidase, or the polymerase is a DNA polymerase or an RNA polymerase.

Proteases degrade proteins, un-specifically or at specific sites. Almost all pharmacologically relevant ones have very narrowly defined specific substrates, and their activity is most often measured by directly measuring cleavage product or generation of (fluorescent) light after cleavage of synthetic substrates. Assays are available for serine proteases (Calbiochem, Palo Alto, CA, and see Berdichevsky et al., J. Virol. Methods, 107:245-255 (2003), for systeine proteases (See: Schulz et al., Mol. Pathol., 51:222-24 (1998) and Selzer et al., PNAS, 96:11015-11022 (1999)), for aspartic acid proteases (Geno Tech, Inc. at www.genotech.com) and for zinc peptidases (see Evans et al., J. Biol. Chem., 278:23180-23186 (2003)).

Both (regulatory) DNA-methylases and (biosynthetic) protein methylases that are drug targets. (See: Jonassen and Clarke, J. Biol. Chem., 275:12381-12387 (2000); Jackson et al., Nature, 416:556-560 (2002)).

Most HDAC (histone deacetylase) assays use colorimetric or fluorometric (synthetic) substrates. Standard assays are for binding, especially molecular size changes, blocking a specific site, and effects on transcription or downstream reactions (if DNA or RNA is the direct target of a drug). A commercial assay is available from Vinci Biochem (at www.vincibiochem.it).

In another specific embodiment, the biological activity is a membrane transport activity, preferably wherein the polypeptide is a cation channel protein, an anion channel protein, a gated-ion channel protein or an ABC transporter protein. Drug effects on the activity of transporter and channel proteins are screened by measuring increase or decrease of the ((radio-)labeled) transported entity inside or outside the cell, in cell-based assays, ATP consumption (in the case of ATPases), or changes in cell membrane

potential. Assays employing such proteins are available, such as for ABC transporter (see: Marcil et al., Lancet, 354:1341-46 (1999) and for ion channels (from Evotec OAI, at www.evotecoai.com and from PharmaLinks, at www.pharmalinks.org/research/cellsignalling).

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In one embodiment, the polypeptide is an integrin (the signal transduction pathways elicited by the integrins are slow and not very well characterized, hence most assays are either just binding assays or measure downstream biological phenomena (such as migration, invasion, etc.) (See: Ganta et al., Endocrinology, 138:3606-3612 (1997); Sim et al., J. Biomed. Mater. Research, 68A:352-359 (2004); and Weinreb et al., Anal. Biochem., 306:305-313 (2002)), or a Cytochrome P450 enzyme (almost all cytochrome assays require knowledge of what the substrate is and measure conversion of substrate (free or (radio-)labeled) or generation of product; useful C14-labeled Amersham **Biosciences** at available from substrates are www1.amershambiosciences.com), or a nuclear hormone receptor (Assays available from Discoverx, Fremont, CA, such as an estrogen assay; also see Rosen et al., Curr. Opin. Drug. Discov. Devel., 6:224-30 (2003)).

In one preferred embodiment, the biological activity is a receptor activity, preferably where the receptor is a G-protein-coupled receptor (GPCR).

GPCRs are transmembrane proteins that wind 7 times back and forth through a cell's plasma membrane with a ligand binding site located on the outside of the membrane surface of the cell and the effector site being present inside the cell. These receptors bind GDP and GTP. In response to ligand binding, GPCRs activate signal transduction pathways which induce a number of assayable physiological changes, e.g., an increase in intracellular calcium levels, cyclic-AMP, inositol phosphate turnover, and downstream gene transcription (directly or via reporter-assays) along with other translocation assays available for measuring GPCR activation when the polypeptide

encoded by a gene of the invention is a GPCR. Thus, such proteins work through a second messenger. The result is activation of CREB, a transcription factor that stimulates the production of gene products. One useful assay is the so-called BRET2/arrestin assay, useful in screening for compounds that interact with GPCRs. (See: Bertrand et al, J. Recept. Signal Transduct Res., 22:533-41 (Feb.-Nov. 2002)). In addition, numerous assays are commercially available, such as the Transfluor Assay, available from Norak Biosciences, Inc. (www.norakbio.com) or ArrayScan and KineticScan, both from Cellomics, or assays from CyBio (Jena, Germany).

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Assays useful with the invention are usually set up to screen for agonists or antagonists after adding ligand, but effects on most of these parameters can be measured whether or not the ligand for the receptor is known. Such assays may involve radioligand-binding assays. Activation of the majority of GPCRs by agonists leads to the interaction of beta-arrestin (a protein that is involved in receptor desensitization and sequestration) with the receptor, which is measurable by fluorescence energy transfer

The disclosure of all journal articles, or other publications, referred to herein are hereby incorporated by reference in their entirety.

In one embodiment, the polypeptide is in a solution or suspension and contact with the test compound is by direct contact between the test compound and the protein molecule. Alternatively, the polypeptide may be in a cell and the test compound may have to diffuse into the cell in order to contact the polypeptide. In an alternative embodiment, the test compound may be contacted with a cell that contains or expresses the polypeptide but the test compound may have no direct contact with the polypeptide. In stead, the test compound may act to induce production and/or activity of a different compound, such as an intracellular second messenger that serves to contact the polypeptide and modulate or change the biological activity of this polypeptide.

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In accordance with the foregoing, the method of the present invention includes cancer modulating agents that are themselves either polypeptides, or small chemical entities, that affect the cancerous process, including initiation, suppression for facilitation of tumor growth, either *in vivo* or *ex vivo*. Such agents may also be antibodies that react with one or more polypeptides encoded by genes present in the amplicons of the invention.

In keeping with the disclosure herein, the present invention also relates to a method for treating cancer comprising contacting a cancerous cell with an agent having activity against an expression product encoded by a gene mapping within regions of chromosomal interest.

The method of the present invention includes embodiments of the above-recited method wherein said cancer cell is contacted *in vivo* as well as *ex vivo*, preferably wherein said agent comprises a portion, or is part of an overall molecular structure, having affinity for said expression product. In one such embodiment, said portion having affinity for said expression product is an antibody.

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In one embodiment of the present invention, a chemical agent, such as a protein or other polypeptide, is joined to an agent, such as an antibody, having affinity for an expression product of a cancerous cell, such as a polypeptide or protein encoded by a gene related to the cancerous process, especially a gene mapping to an amplicon as disclosed herein In a specific embodiment, said expression product acts as a therapeutic target for the affinity portion of said anticancer agent and where, after binding of the affinity portion of such agent to the expression product, the anti-cancer portion of said agent acts against said expression product so as to neutralize its effects in initiating, facilitating or promoting tumor formation and/or growth. In a separate embodiment of the present invention, binding of the agent to said expression product may, without more, have the effect of deterring cancer

promotion, facilitation or growth, especially where the presence of said expression product is related, either intimately or only in an ancillary manner, to the development and growth of a tumor. Thus, where the presence of said expression product is essential to tumor initiation and/or growth, binding of said agent to said expression product will have the effect of negating said tumor promoting activity. In one such embodiment, said agent is an apoptosis-inducing agent that induces cell suicide, thereby killing the cancer cell and halting tumor growth.

Many cancers contain chromosomal rearrangements, which typically represent translocations, amplifications, or deletions of specific regions of genomic DNA. A recurrent chromosomal rearrangement that is associated with a specific stage and type of cancer always affects a gene (or possibly genes) that play a direct and critical role in the initiation or progression of the disease. Many of the known oncogenes or tumor suppressor genes that play direct roles in cancer have either been initially identified based upon their positional cloning from a recurrent chromosomal rearrangement or have been demonstrated to fall within a rearrangement subsequent to their cloning by other methods. In all cases, such genes display amplification at both the level of DNA copy number and at the level of transcriptional expression at the mRNA level.

In accordance with the present invention, said functionally related genes are genes modulating the same metabolic pathway or said genes are genes encoding functionally related polypeptides. In one such embodiment, said genes are genes whose expression is modulated by the same transcriptional activator or enhancer sequence, especially where said transcriptional activator or enhancer increases, or otherwise modulates, the activity of a gene mapping to one of the amplicons of the invention.

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The present invention also relates to a process that comprises a method for producing a product, such as test data, comprising identifying an

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agent according to one of the disclosed methods for identifying such an agent (i.e., the therapeutic agents identified according to the assay procedures disclosed herein) wherein said product is the data collected with respect to said agent as a result of said identification process, or assay, and wherein said data is sufficient to convey the chemical character and/or structure and/or properties of said agent. For example, the present invention specifically contemplates a situation whereby a user of an assay of the invention may use the assay to screen for compounds having the desired enzyme modulating activity and, having identified the compound, then conveys that information (i.e., information as to structure, dosage, etc) to another user who then utilizes the information to reproduce the agent and administer it for therapeutic or research purposes according to the invention. For example, the user of the assay (user 1) may screen a number of test compounds without knowing the structure or identity of the compounds (such as where a number of code numbers are used the first user is simply given samples labeled with said code numbers) and, after performing the screening process, using one or more assay processes of the present invention, then imparts to a second user (user 2), verbally or in writing or some equivalent fashion, sufficient information to identify the compounds having a particular modulating activity (for example, the code number with the corresponding results). This transmission of information from user 1 to user 2 is specifically contemplated by the present invention.

In accordance with the **f**oregoing, the present invention relates to a method for producing test data with respect to the anti-neoplastic activity of a compound, such as a test compound as defined herein, comprising:

- (a) identifying a test compound as having anti-neoplastic activity using a method of the invention, such as measuring the biological activity of a polypeptide encoded by a gene of Table 3 (SEQ ID NO: 1-3049), and
- (b) producing test data with respect to the anti-neoplastic activity of said test compound sufficient to identify the chemical structure of said test compound.

In another embodiment, the present invention provides a method for monitoring the progress of a cancer treatment, such as where the methods of the invention permit a determination that a given course of cancer therapy is or is not proving effective because of an increased or decreased expression of a gene, or genes, mapping to an amplicon as disclosed herein. For example, where there is an increased copy number of one or more of said genes monitoring of such genes can predict success or failure of a course of therapy, such as chemotherapy, or predict the likelihood of a relapse based on elevated activity or expression of one or more of these genes following such course of therapy.

In accordance with the foregoing, the present invention contemplates a method for determining the progress of a treatment for cancer in a patient afflicted with cancer, following commencement of a cancer treatment on said patient, comprising determining in said patient a change in expression of one or more genes, preferably more than one, corresponding to a gene of Table 3 or encoding a polypeptide or transcript of such a gene, or genes compared to expression of said one or more determined genes prior to commencement of said cancer treatment, wherein a change in expression, especially a decrease in expression, indicates positive effects of such treatment, thereby determining the progress of said treatment.

In a preferred embodiment, the detected change in expression is a decrease in expression. In another preferred embodiment, the cancer treatment is treatment with a chemotherapeutic agent, especially an agent that modulates, preferably decreases, expression of a gene identified herein, such as where said agent was first identified as having anti-neoplastic activity using a method of the invention. Thus, in accordance with this aspect of the present invention, a patient, or even a research animal, such as a mouse, rat, rabbit or primate, afflicted with cancer, including a cancer induced for research purposes, is introduced to a cancer treatment regimen, such as

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administration of an anti-cancer agent, including one first identified as having anti-neoplastic activity by one or more of the screening methods disclosed herein. The progress and success or failure of such treatment is subsequently ascertained by determining the subsequent expression of one or more, preferably at least 3, or 5, or 10, of genes mapping to one or more of the amplicons disclosed herein, preferably to the same amplicon, or that encodes a transcript or polypeptide of such a gene following said treatment. In a preferred embodiment, a treatment that reduces said expression is deemed advantageous and may then be the basis for continuing said treatment. The methods of the invention thereby provide a means of continually monitoring the success of the treatment and evaluating both the need, and desirability, of continuing said treatment. In addition, more than one said treatment may be administered simultaneously without diminishing the value of the methods of the invention in determining the overall success of such combined treatment. Thus, more than one said anti-neoplastic agent may be administered to the same patient and overall effectiveness ascertained by the recited methods.

In accordance with the foregoing, the present invention also contemplates a method for determining the likelihood of survival of a patient afflicted with cancer, following commencement of a cancer treatment on said patient, comprising determining in said patient a change in expression of one or more genes, preferably more than one, corresponding to a gene of Table 3 or encoding a polypeptide or transcript of such a gene, or genes, compared to expression of said one or more determined genes prior to commencement of said cancer treatment, wherein a change in expression, es pecially a decrease in expression, indicates positive and life-extending effects of such treatment, thereby determining the likelihood of survival of said treatment.

In a preferred embodiment, the detected change in expression is a decrease in expression and said determined gene, or genes, may include 2, 3, 5, 10 or more of the genes described herein. Thus, the methods of the invention may be utilized as a means for compiling cancer survival statistics

following one or more, possibly combined, treatments for cancer as in keeping with the other methods disclosed herein.

The genes of the amplicons, or regions of interest, identified herein also offer themselves as pharmacodynamic markers (or as pharmacogenetic and/or surrogate markers), such as for patient profiling prior to clinical trials and/or targeted therapies, including combination treatments, resulting from the identification of these genes as valid gene targets for chemotherapy based on the screening procedures of the invention. In one embodiment thereof, the likelihood of success of a cancer treatment with a selected chemotherapeutic agent may be based on the fact that such agent has been determined to have expression modulating activity with one or more genes identified herein, especially where said genes have been identified as showing elevated expression levels in samples from a prospective patient afflicted with cancer. Methods described elsewhere herein for determining cancerous status of a cell may find ready use in such evaluations.

It should be cautioned that, in carrying out the procedures of the present invention as disclosed herein, any reference to particular buffers, media, reagents, cells, culture conditions and the like are not intended to be limiting, but are to be read so as to include all related materials that one of ordinary skill in the art would recognize as being of interest or value in the particular context in which that discussion is presented. For example, it is often possible to substitute one buffer system or culture medium for another and still achieve similar, if not identical, results. Those of skill in the art will have sufficient knowledge of such systems and methodologies so as to be able, without undue experimentation, to make such substitutions as will optimally serve their purposes in using the methods and procedures disclosed herein.

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The present invention will now be further described by way of the following non-limiting example. In applying the disclosure of the example, it

should be kept clearly in mind that other and different embodiments of the methods disclosed according to the present invention will no doubt suggest themselves to those of skill in the relevant art.

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EXAMPLE

Cancerous cells that over-express one or more genes mapping to the amplicons disclosed herein, are grown to a density of 10⁵ cells/cm² in Leibovitz's L-15 medium supplemented with 2 mM L-glutamine (90%) and 10% fetal bovine serum. The cells are collected after treatment with 0.25% trypsin, 0.02% EDTA at 37°C for 2 to 5 minutes. The trypsinized cells are then diluted with 30 ml growth medium and plated at a density of 50,000 cells per well in a 96 well plate (200 μ l/well). The following day, cells are treated with either compound buffer alone, or compound buffer containing a chemical agent to be tested, for 24 hours. The media is then removed, the cells lysed and the RNA recovered using the RNAeasy reagents and protocol obtained from Qiagen. RNA is quantitated and 10 ng of sample in 1 μl are added to 24 μl of Taqman reaction mix containing 1X PCR buffer, RNAsin, reverse transcriptase, nucleoside triphosphates, amplitaq gold, tween 20, glycerol, bovine serum albumin (BSA) and specific PCR primers and probes for a reference gene (18S RNA) and a test gene (Gene X). Reverse transcription is then carried out at 48°C for 30 minutes. The sample is then applied to a Perlin Elmer 7700 sequence detector and heat denatured for 10 minutes at 95°C. Amplification is performed through 40 cycles using 15 seconds annealing at 60°C followed by a 60 second extension at 72°C and 30 second denaturation at 95°C. Data files are then captured and the data analyzed with the appropriate baseline windows and thresholds.

The quantitative difference between the target and reference genes is then calculated and a relative expression value determined for all of the samples used. This procedure is then repeated for each of the target genes in

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a given signature, or characteristic, set and the relative expression ratios for each pair of genes is determined (i.e., a ratio of expression is determined for each target gene versus each of the other genes for which expression is measured, where each gene's absolute expression is determined relative to the reference gene for each compound, or chemical agent, to be screened). The samples are then scored and ranked according to the degree of alteration of the expression profile in the treated samples relative to the control. The overall expression of the set of genes relative to the controls, as modulated by one chemical agent relative to another, is also ascertained. Chemical agents having the most effect on a given gene, or set of genes, are considered the most anti-neoplastic.

SEQUENCE LISTING ON CD-ROM ONLY

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The sequences disclosed herein as SEQ ID NO: 1-3049 in the sequence listing are contained on compact disc (CD-ROM) only (denoted as Filename: Avalon 237 (5,279 kB), 4 copies of which appear on discs denoted Copy 1, Copy 2, Copy 3 and CRF, and which discs were generated on 7 March 2005), which accompanies this application and the contents of said CD-ROMs are hereby incorporated by reference in their entirety. These sequence numbers correspond to cDNA sequences derived from the genes identified in Table 3.

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Table 3 - / Amplicon	Table 3 – Amplicon Identification Amplicon Transcript Id	Name	Chromosome	bpstart	pbend
ΑŢ	ENST00000303924	HAS2	∞	258293	59816
Z Z Z	ENSESTT0000046662	ىد	∞	258593	22609
	STT0000004666		∞	260852	261006
1 7 Z	TT0000004		Φ	2264059	2265339
7.7. 7.7.	00000328524		∞	2373811	2373895
	00		8	2375017	2392021
T 7	00000314393	NM 014943	∞	2375057	2394333
7.7.		1	∞	2378972	2379035
T 7			∞	2392188	2394333
T C/			8	2398393	2398813
7.7.	\sim		∞	2398393	2401120
7.7.T. (Z.)	, _		8	2398393	2401120
7. Z	00259512	NM 024295	∞	2398403	2401108
77T	0000004711	Ì	∞	2398404	2399032
7.7.7 L \(\sigma\)			8	2398768	2399954
7.7.	000004711		ω	2399151	2401120
7.7. Z 7	000006561		8	2404156	2406247
7.1. D.1	000287380	NM 145647	∞	124041598	241207
	SESTT0000006	ì	Φ	2404207	2406621
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NM_012279	FGER4 NM_022963	,	NSDT	RAB24 PX19_HUMAN	Q96ME3 MXD3 LMAN2 RGS14
02619 00002 00002 00002 00002	ST00000292408 ST00000292410 SESTT00000025	SESTT000000025 SESTT000000025 SESTT000000025	298507 0000025 0000025 0000025 312855 0000025	SESTIOU000223270 STOOOO0303270 SESTTOOOOO025 STOOOO0303204	30318 30316 30312 00002 30306
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76779454 1767805 76792400 17679446 76792400 17680680 76804912 17680614 76808126 17680853 76810246 17681748	76834655 17684137 76834669 17684463 76834669 17684900 76834669 17684900 76834669 17684900	6834797 176849 6841092 176844 6841092 176849 6841092 176849 6842854 176849 6842854 176849 6842854 176849	76854894 17686413 76854894 17686413 76864466 17688146 76891199 17690541 76891449 17690431 76891939 17703167 76897221 17703816
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76897716 1770382	69043	76898906 17690431	76909731 17691609	76911807 17691767	76919402 17692466	76926890 17694379	76926890 17696163	68 177094	76999291 17700262	76999295 17713328	76999295 17713609	76999300 17700320	76999308 17713608	77000737 17700321	77000783 17713634	77001245 17713671	77007252 17715069	77023996 17703819	77024173 17703819	77024246 17703711	77024246 17703711	77031099 17703711	77031469 17703819	77031684 17703720	77031702 17703711	77042509 17704886	77044585 1770	77045241 17705044	77045345 17705098
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	Q96C91	Q9BXB8	Q9BQB3	NM 024872	$\overline{\text{DDX}41}$		NM 019057					NM 017510			,			NM_005451	1	014250	Q9BXB9	Q96C91			Q9BXB8		NM 024872		
STT000000	T00000330641	33198	31294	27482	33050	0000	329540	ENSESTT00000026015	0000260	0000260	0000260	32817	0000260	0000357	0000357	0000357	0000357	333469	00000	292374	3315	33186	0000358	0000003580	ST00000332347	ST000003317(ST000003333	SESTT000000357	0003579
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DDX41	NM_019057	NM_017510 B4GALT7	Q9HAI8	NM_173663	Q8TE30	THOC3 09H7L9	PROP1	Y341_HUMAN YE01_HUMAN
STT0000 000033 TT0000 TT0000	0274788 00000357 00000357	00000035 0332598 0029410	000003	0303108 0324610	0000035 0329355 0331417 0328082	033221	000000000000000000000000000000000000000	ST0000033264 ST0000027460 SESTT0000003 ST0000031337
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NOLA2 NM_022471 HNRPAB		NM_004499	NM_032921
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591731 17 92740 178 17905 178 43326 179 90766 179 99924 179 00164 179 00278 179 33252 179	79140510 17914058 79148300 17914836 79150871 17915475 79150871 17915475 79150871 17916039	79150872 17916035 79151147 17916039 79151147 17916039 79151282 17915475 79152814 17915985 79154867 17916036 79157887 17916036	79176906 17917744 79184188 17918686 79184188 17918764 79215326 17923146
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ADAMTS2	NM_030970	HNRPH1	Q8NA96 Q86VE1.
ENSESTT0000274609 ENSESTT0000025804 ENSESTT0000035851 ENSESTT0000035852 ENSESTT0000035853 ENSESTT0000035855 ENSESTT0000035855 ENSESTT0000035855 ENSESTT0000035855	ST00000319571 ST00000258707 SESTT0000003591 SESTT0000003590	326748 0000359 0000359 0000359 0000359 0000359	ST0000033187 SESTT0000003 ST0000032885 SESTT0000003
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79215692 1792176 79230857 17923135 79235589 17924504 79235589 17926755 79240421 17926755 79243792 17926755 79246533 17925639	79269772 17931394 79303154 17930785 79314421 17931499 79330648 17933317	179330774 179333175 179330774 179333175 179332243 179333174 179334262 179343246 179334633 179338133 179334633 179338133 179334633 179338133 179334883 179338133 179334883 179343595 179334883 179343595 179335007 179343595 179335007 179343595
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CANX	MAML1 NM_024978 LTC4S	MGAT 4B
2915 2915 0003 0003 0003 0003	92599 92599 0003586 98607 92596	ENSESTTO000035868 ENSESTT0000035869 ENSESTT0000035867 ENSESTT0000035867 ENSESTT0000035901 ENSESTT00000035902 ENSESTT00000035903 ENSESTT0000035903 ENSESTT0000035895 ENSESTT0000035896 ENSESTT0000035896 ENSESTT0000035897 ENSESTT0000035897 ENSESTT0000035897 ENSESTT0000035897 ENSESTT0000035899
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7567 179373 599 1793733 111 1793733 136 1793735 135 1793954 135 179444 135 179402 135 179404 147 179444 144 179404 144 179444 144 179444 144 179444 144 179608 150 179608 168 179608 168 179608 1790 179608 1790 179608 1790 179608 1791 179745 1791 179745	79773046 17981722 79773046 17981722 79783749 17979844
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ENSESTTO000035871 ENST0000292588 ENST00000292586 ENST0000035893 ENST00000328625 ENST00000328625 ENST00000328625 ENSESTT0000035892 ENSESTT0000035889 ENSESTT0000035889 ENSESTT0000035886 ENSESTT0000035886 ENSESTT0000035884 ENSESTT0000035884 ENSESTT00000035889 ENSESTT0000035889 ENSESTT0000035889 ENSESTT0000035889 ENSESTT0000035889 ENSESTT0000035889 ENSESTT0000035889 ENSESTT0000035889 ENSESTT0000035881 ENSESTT0000035883 ENSESTT0000035883 ENSESTT0000035883 ENSESTT0000035883	SESTIO000057533 ST00000057533 ST00000316123 SESTT000000358
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79794621 1797966 79816486 17982853 79837361 17987526 79837891 17986831 79861517 17986748 79868152 17988998	30065924 18011086 30065968 18008726 30065968 18010118 30112873 18011315 30126767 18012814	126768 1801281 139821 1801480 145626 1801862 162667 1801666 166890 1801862 229572 1802304 275785 1802767 327203 1803286	80327543 18033948 80327543 18033948 80328296 18032963 80329112 18033950 80329332 18034054 80332068 18035222 80332092 18033942 80332309 18034535
വ വവവവവ	ភាពាលបាល	រប្រាប្យម្នាប់	വവവവവവവവ
GFPT2	NM_015455 Q8TAJ0	SCGB3A1 ELT4 Q8NHB0 Q8NGV0	MGAT1 Q8NBL8
3280 0003 0003 0003 0003	61951 61951 000356 000356 32929 000356	00000000	33055 00035 00035 00035 00035 00035 00035
A A A A A A A A A A A A A A A A A A A	A A A A A A A A A A A A A A A A A A A	A3 A3 A3 A3 A3	A3 A3 A3 A3 A3

0344545 1803467 345508 18035220 345511 18034679 384273 18039722 384335 18039794	80385559 18038776 80386417 18038813 80387577 18039721	21 18048 55 18044 11 18048	80525529 18054302 80582152 18059022 80589782 18059196	80590141 18059818 80592305 18059597	80650802 18063/31 80650805 18065192 80661176 18066196	80691605 18069255 80728586 18073109 80731275 18073681	80734864 18073976 80739916 18074178	80760899 18077204 80760917 18077246	80769651 18077247 80770071 18077247 80773587 18078058
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	NM_152283	NM_024850	BTNL3 NM_152547	Q8N324		Q8NGV1 ,		TRIM/ Q96Q10 TRIM41	GNB2L1
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NM_022907	TRIM52		O4E3_HUMAN	FLT1-001 FLT1		bA57H24.1-001 C13orf12 bA97E23.1-001 bA97E23.1-002
SESTT000000035 ESTT0000000356 ESTT000000356 T00000327725	0000035 0000035 0327767 0000035	0000035 0000035 0000035	33864 00035 00035 32522	13000 82397 00037 00037		13000 13000 13000 13000
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27051	03499	705047	705033	107669	709073	709110	708298	708527	709111	709615	709527	715107	787554	787589	762269	762269	762269	767323	768005	787587	786944	785988	785988	785988	796772	790832	789164	789454	790286
27031	33127	703287	704448	707220	707285	707285	707338	707340	708547	709452	709484	715069	739745	739745	761151	761176	761192	765384	767884	780076	780092	784868	784903	784903	788154	788661	788900	788900	789455
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			•	bA97E23.2-002	NM 181785	bA97E23.2-001				bA97E23.3-001		bA161P17.1-001	Q8N5E2	bA274A8.1-002	.3-00	bA351N4.3-002	00-		bA351N4.2-001			Q8N642	bA274A8.2-001		SLC7A1-001	SLC7A1	SLC7A1-002		
	ENSESTT00000037330		ESTT0000003	0001300071	0026	001300	000003734	00003	0000373	0013000	0000373	0001300072	025528	001300	1300072	00072	1300072	000373	1300072	1300073	000003733	0323380	00013	0000373	013000	0266949	001300	NSESTT0000003733	ESTT0000003733
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0000 0000 0130 3303 2553	ENST00000310635 OTTHUMT00013000746 ENST0000241470 ENSESTT00000037445 ENSESTT00000037444	074 074 743	1 074 075 075 075	ENSESTT00000037442 ENST00000261628 ENSESTT00000037440 ENSESTT00000037441 ENSESTT00000037441	THUMT0001300 ST0000031901 THUMT0001300 THUMT0001300
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287378 373628 374928 374910 380079 382062 382062	383801 383801 383644 383644 383807	28835401 28835401 28836526 28989872 28836793 28838651 28838651 28915034 28915034 28915034 28915034 29031686 29031686 29031686
87146 372987 372987 373531 374614 380009 380009 381854	383199 383398 383356 383363 383363	28834423 28834483 28834675 28834713 28835448 28835448 28835448 28911734 28913780 28925807 28989830 28989830 28989830 28989830 28989830 28989830 28989830
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001300076 001300076 001300076 001300076 0302464 001300079	01300077 255320 00003743 01300077 01300077	ENSESTTO000037435 OTTHUMT00013000781 OTTHUMT00013000782 ENSESTT0000037434 OTTHUMT00013000778 OTTHUMT00013000796 OTTHUMT00013000796 OTTHUMT00013000801 ENST00000255304 OTTHUMT00013000800 ENSESTT0000037433 ENSESTT00000037433
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	1300081	bA252M21.1-001	13	925468	925553
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0		NM 032849	13	927832	929770
\circ	130	bA252M21.2-001	13	927832	929770
OTTHUMT00	1300081	bA252M21.2-002	13	927884	929658
0	04239		13	928953	929796
ENSESTIO0	00042		13	930280	930362
00	00081	bA252M21.3-001	13	930281	930361
OTTHUMT000	300081	bA252M21.4-001	13	930363	930472
0	1300081	bA252M21.4-002	13	930376	930433
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	00		13	932900	934727
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THUMTOOO	1300082	bA252M21.7-001	13	936729	936827
TTHUMTOOO	130008	3.1-00	13	947123	948783
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ESTT00	0004		13	950875	951131
STT00	0000424		13	950875	952023
STTOO	0000424		13	950875	952023
\circ	00004		13	950875	952023
ENSESTT00	0000424		13	950875	952023
TTOO	000042403		13	950875	952055

295205	29520554	952055 952055	952062	952062	952062	952062	952388	952388	952388	952388	920366	29510705	953406	953406	953406	951104	952023	952023	952055	952055	952062	952062	952388	952388	953371	953371	951131	952023	952055
295087	75	320872	950875	950875	950875	950875	95087	950875	95087	950875	950876	9	920816	920876	920876	950900	950900	950900	950900	950900	950900	950900	950900	920900	950945	950945	950964	951041	951041
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TABLE 3 (Continued)

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	551446	552314	552405	554399	554401	554401	556820	557098	557099	560253	563073	563073	563105	563146	566634	566637	567097	567432	570307	570311	570311	570312	75703136	570314	570314	570315	571150	7115	574357
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394889		ESTT00	0	ENSESTT00000040213	OTTHUMT00007006552	ENST00000248553	OTTHUMT00007006186	ENST00000307630	ENSESTT00000040235	325	ENST00000275560	OTTHUMT00007006188	ENSESTT00000040234	ENST00000297799	OTTHUMT00007006555	ENST00000257652	ENSESTT00000040214	ENSESTT00000040215	$\overline{\Box}$	0004021	000040	ENSESTT00000040219	ENSESTT00000040220	OTTHUMT00007006196	ENST00000324432		0	0329896	00
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76243673 76255577 76257204 76260312 76263908 76264978	76266095 76266148 76269559 76271927 76279424	631315 632540 633088 635135 635680	76356814 76364104 76437484 76437495 76437634
Hs_7_c1202 Q86WY7 mfhmh_gw11359887 .75188365.75365376	- J. 9e-	Hs_7_c1203 mbhmh_h_75248517 76148516_m 19731738_198	Hs_7_c1204 mbax_nh_gi17389564 FGL2 mbhmh_h_75248517 76148516_m 19731738_198
ENSESTT00000037258 ENSESTT0000037261 ENSESTT0000037259 OTTHUMT0000285792 ENSESTT0000037292 OTTHUMT00007006602	003 003 003 003	ENSESTT000007087289 OTTHUMT00007006666 OTTHUMT00007006666	ENSESTT000007007332 ENSESTT0000037260 OTTHUMT00007006412 ENST0000248598 ENSESTT0000037287 OTTHUMT00007006667
A7 A7 A7 A7 A7	A7 A7 A7 A7	A A A A A A A A A A A A A A A A A A A	A77 A77 A77 A77 A77

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A9 A9 A9 A9	A9 A9	A9	A9	A9	A9 A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9

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A9	000600643	GLO1-001 6	057	871777
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A9	ENSESTT00000028264	9	38690577	871778
A9	ENSESTT00000028262	9	86	86991

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217 A 9	0600646		lo	956844	956957
6 K	0002828		lo	959780	959958
7 A 9	060064	dJ1043E3.1-002	lo	959780	961089
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0 K	000028		lo	970626	973992
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9 A	000002828		9	990320	991201
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